REMARKS

This amendment is submitted in response to the Official Action mailed March 12, 2008. Claims 1-32 are pending. Claims 1, 6, 22, and 26-32 are amended to more particularly point out and distinctly claim the invention. In particular, claim 1 is amended to recite that the polymeric coating comprises at least one enteric polymer coating material selected from cellulose acetate phthalate, cellulose acetate trimaletate, hydroxyl propyl methylcellulose phthalate, polyvinyl acetate phthalate, Eudragit poly acrylic acid, Eudragit S, Eudragit L, polyvinyl acetaldiethylamino acetate, hydroxypropyl methylcellulose acetate succinate, cellulose acetate trimellitate and shellac. Support for this amendment is found at, for example, paragraph [0033] of the originally-filed application. Additionally, claims 6 and 22 are amended to correct typographical errors. Also, claims 26-32 are amended so the language more closely resembles that of paragraph [0014] of the originally-filed application. No new matter is added. In view of the above claim amendments and the following remarks, reconsideration by the Examiner and allowance of the application is respectfully requested.

Turning to the Official Action, claim 4 is objected to under 37 CFR 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. Specifically, the Office Action alleges that claim 4 does not limit claim 3 because "hemifumarate and fumarate have the same formula." (Office Action, page 3). However, claim 3 recites "a pharmaceutically acceptable salt of bisoprolol," which is a genus for the hemifumarate species. Therefore, this rejection is respectfully traversed because claim 4 further limits claim 3.

Claims 6 and 22 are objected to because of typographical errors. As noted above, these claims are amended to correct these errors.

Claims 26-32 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Office Action alleges that the phrases "enriched in the (S)-enantiomer" and "enriched (S)-bisoprolol" are not supported by the as-filed application. However, paragraph [0014] supports the concept of (S)-bisoprolol. Paragraph [0014] states that "bisoprolol refers to both racemic and enantiomeric forms of

bisoprolol." It is known in the art that the enantiomeric forms of bisoprolol are (S)-bisoprolol and (R)-bisoprolol. Therefore, this rejection is respectfully traversed.

Claims 1-32 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Office Action alleges that the phrases "being effective to achieve" in claim 1 and "effective to prevent" in claim 2 do not alone show patentable distinction. However, claim 1 is amended to further define the polymer coating material. Additionally, the Office Action alleges that the phrase "at least" in claims 1 and 2 is interpreted to have no upper limit. However, the phrase "at least" refers to an initial lag time within a twenty-four hour time period. Therefore, "at least" is not open-ended. Therefore, this rejection is respectfully traversed.

Claims 1-32 are rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,137,733 to Noda et al. in view of U.S. Patent No. 5,580,578 to Oshlack et al. Applicants' claimed formulation is a multiparticulate bisoprolol formulation wherein each particle comprises a core of bisoprolol or a pharmaceutically acceptable salt thereof surrounded by a polymeric coating comprising at least one enteric polymer coating material selected from cellulose acetate phthalate, cellulose acetate trimaletate, hydroxyl propyl methylcellulose phthalate, polyvinyl acetate phthalate, Eudragit poly acrylic acid, Eudragit S, Eudragit L, polyvinyl acetaldiethylamino acetate, hydroxypropyl methylcellulose acetate succinate, cellulose acetate trimellitate and shellac. The enteric polymer coating materials exhibit a pH-dependent dissolution profile.

Noda et al. makes clear that its formulations are designed for dissolution that is independent of the pH. See, for example, the Abstract ("dissolution pattern irrespective of the pH of a dissolution medium") and the Background of the Invention ("An object of this invention . . . and the rate of the dissolution of the medicinal compound does not depend on the pH of a medium for the dissolution"). The polymers that Noda et al. exemplifies are recognized in the art as pH-independent. Also, the experiments described in Noda et al. show a formulation that exhibits a pH-independent drug release profile. Clearly, pH-independence is at the very heart of the Noda et al. teaching.

The present invention, on the other hand, relies on the use of a polymer system for which the dissolution depends on the pH of the medium. Applicants' claimed invention is specifically formulated to exhibit a release of bisoprolol that is affected by the pH of the medium. This is very clearly different from the Noda et al. formulation.

That Noda et al. fails to suggest the formulations of the subject invention is further supported by the stark differences in the correlation between *in vitro* dissolution delays and delays in *in vivo* bioavailability obtained with the Noda et al. formulations on one hand, and the correlation shown when pH-independent polymers are used in conjunction with the formulations of the invention, on the other hand. As indicated by Figures 2 and 3 of Noda et al., the Noda et al. formulations show substantially the same delay *in vitro* and *in vivo*. The Noda et al. formulations show a delay of about 8 hours prior to dissolution *in vitro* (Figure 2) and essentially no measurable plasma concentration *in vivo* until after about 8 hours from administration (Figure 3).

In contrast to the pH-independent formulations of diltiazem described in Noda et al., which shows matching *in-vitro* delays and *in-vivo* delays, the pH-independent formulation examples in the present application show that the *in-vitro* and *in-vivo* delays for bisoprolol are markedly different e.g., Formulation D (Example 3) shows an *in-vitro* delay of 2-4 hours (Table 1) yet results in an *in-vivo* delay of 8-14 hours (Table 5).

However, when bisoprolol is formulated in a pH-dependent system (Example 5), as presently claimed an *in-vitro* delay of 4-6 hours (Table 1) results in a matching *in-vivo* delay of 4-6 hours (Table 5). There is no way that one skilled in the art could predict from Noda et al. that employing a pH-independent polymer in conjunction with the formulation of the subject invention would lead to formulations showing different delays *in vivo* and *in vitro*, while employing pH-dependent polymers, as presently claimed, would show comparable delays *in vitro* and *in vivo*.

Oshlack et al. does not cure the deficiencies of Noda et al. The Office Action relies on Oshlack et al. for its purported disclosure of "a controlled release formulation wherein a barrier layer is incorporated between the medicinal core and the acrylic coating layer." (Office Action, page 9). Even assuming Oshlack et al. does disclose such a barrier, this does

not guide one of skill in the art to a pH-dependent polymer system as presently claimed. Thus, the combination of Noda et al. with Oshlack et al. does not teach or suggest the presently claimed invention. Therefore, this rejection is respectfully traversed.

CONCLUSION

In view of the above claim amendments and the foregoing remarks, this application is believed to be in condition for allowance. Reconsideration is respectfully requested. However, the Examiner is requested to telephone the undersigned if there are any remaining issues in this application to be resolved.

Finally, if there are any additional charges in connection with this response, the Examiner is authorized to charge Applicant's deposit account number 50-1943 therefor.

Respectfully submitted,

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